

## GABAergic interneuron dysfunction impairs hippocampal neurogenesis in adult apolipoprotein E4 knockin mice.

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### Public Summary:

Apolipoprotein (apo) E, a protein with three common variants (apoE2, apoE3, and apoE4), is essential for lipid homeostasis. Individuals carrying apoE4 are at higher risk for developing Alzheimer's disease. However, the mechanisms underlying apoE4's contribution to Alzheimer's disease are still unclear. We have investigated the generation of new neurons, called neurogenesis, in mice having no apoE or having human apoE3 or apoE4. We found that neurogenesis is reduced in mice having no apoE and in mice having apoE4. In mice without apoE, increased BMP signaling promoted glial cell differentiation at the expense of neurogenesis. In contrast, in mice with human apoE4, the inhibitory input-mediated maturation of newborn neurons was diminished. Tau phosphorylation, an Alzheimer's disease characteristic, and levels of neurotoxic apoE fragments were both elevated in apoE4 producing neurons concomitant with decreased inhibitory GABAergic neuron survival. Enhancing inhibitory signaling restored neuronal maturation and neurogenesis in mice producing apoE4 to normal levels. These findings suggest that the inhibitory GABAergic signaling can be targeted to mitigate the deleterious effects of apoE4 on neurogenesis.

### Scientific Abstract:

Apolipoprotein (apo) E, a polymorphic protein with three isoforms (apoE2, apoE3, and apoE4), is essential for lipid homeostasis. Carriers of apoE4 are at higher risk for developing Alzheimer's disease. We have investigated adult neurogenesis in mice with knockout (KO) for apoE or with knockin (KI) alleles for human apoE3 or apoE4, and we report that neurogenesis is reduced in both apoE-KO and apoE4-KI mice. In apoE-KO mice, increased BMP signaling promoted glial differentiation at the expense of neurogenesis. In contrast, in apoE4-KI mice, presynaptic GABAergic input-mediated maturation of newborn neurons was diminished. Tau phosphorylation, an Alzheimer's disease characteristic, and levels of neurotoxic apoE fragments were both elevated in apoE4-KI hippocampal neurons concomitant with decreased GABAergic interneuron survival. Potentiating GABAergic signaling restored neuronal maturation and neurogenesis in apoE4-KI mice to normal levels. These findings suggest that GABAergic signaling can be targeted to mitigate the deleterious effects of apoE4 on neurogenesis.

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